

$R^3$  and  $R^4$ ,  $R^4$  and  $R^5$ , or  $R^5$  and  $R^6$  may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

$R^7$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

*B4 cont*  
 $R^9$  is  $-(alk_1)Z$ , wherein  $Alk_1$  is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

$R^8$  and  $R^{10}$  are independently selected from hydrogen and unsubstituted lower alkyl;

one or more pharmaceutically acceptable surfactants; and

one or more pharmaceutically acceptable oils.

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## REMARKS

### **I. INTRODUCTION**

Receipt of the Office Action of March 19, 2003 is acknowledged. Claims 1, 78 and 80 have been amended to more particularly point out and distinctly claim the subject matter Applicants regard as their invention. After amending the claims as set forth above, claims 1, 3 – 5, 7 – 8, 10, 11, 13 – 34, 36, 38 – 48 and 50 – 87 are pending in this application.

### **II. THE OFFICE ACTION**

#### **A. Response to Arguments**

The Examiner states that Applicants' arguments submitted with the December 6, 2002 Response have been considered but not found persuasive/successful in overcoming the rejection under 35 U.S.C § 103(a) over the Tang reference (U.S. Patent No. 5,792,783). For the reasons detailed below, Applicants will show that Tang is not a competent reference for establishing a *prima facie* case of obviousness vis-à-vis the pending claims.

**B. Claim Objections**

The Examiner has objected to claim 78 because the “subletters ‘a.’ and ‘b.’” have periods following them. To overcome the objection, Applicants have followed the Examiner’s kind suggestion of removing the periods after the letters and substituting the periods with parentheses. Reconsideration and withdrawal of the objection is respectfully requested.

**C. Rejections based on 35 U.S.C. § 112, first paragraph**

Applicants acknowledge that the Examiner has withdrawn the rejection of claims 78 and 80 under 35 U.S.C § 112, first paragraph presented in the Office Action dated June 6, 2002.

On page 4 of the Office Action, the Examiner has rejected claims 1, 3 – 5, 7, 8, 10, 13 – 34, 36, 38 – 48 and 50 – 87 under 35 U.S.C, § 112, second paragraph. In light of the amendments to claims 1, 76, 78 and 80, Applicants assert that the rejection is now moot. In particular, Applicants have replaced the “missing”  $R^6$  variable in the formulae in claims 1, 76, 78 and 80. Applicants have also corrected an apparent clerical error which caused the variable  $R^{10}$  not to be defined. Support for the amendment to claims 1, 76, 78 and 80, vis-à-vis  $R_{10}$  may be found on page 65, lines 7 – 12. Withdrawal and reconsideration of the rejection is respectfully requested.

**D. Rejections based on 35 U.S.C. § 102(b)**

Applicants acknowledge that the Examiner has withdrawn the rejection of claim 1 under 35 U.S.C. § 102(b) over Tang (U.S. Patent No. 5,792,783).

**E. Rejections based on 35 U.S.C. § 103**

The Examiner has rejected claims 1 – 84 under 35 U.S.C. § 103 as allegedly unpatentable over Tang (U.S. Patent No. 5,792,783, hereafter, “Tang ‘783”). Applicants respectfully traverse.

Applicants submit that the Tang reference is not a competent reference for the purposes of an obviousness rejection under 35 U.S.C. § 103(a) since this application was

filed on November 21, 2000; that is, after the enactment of the amendments to 35 U.S.C. § 103 under the American Inventors Protection Act (AIPA) of 1999.

As amended, 35 U.S.C. § 103(c) states:

Subject matter developed by another person, which qualifies as prior art only under subsection (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Applicants assert that the claimed invention and the Tang patent were commonly owned by Sugan, Inc. at the time the claimed invention was made. In support of this assertion, Applicants submit herewith a copy of the assignment document(s) for the Tang patent, which issued from U.S. Serial No. 08/655,223, and for the instant application. Thus, under the new law, the Tang patent may not be held as prior art, under 35 U.S.C. § 103, against the claimed invention. Accordingly, reconsideration and withdrawal of the § 103 rejection is respectfully requested.

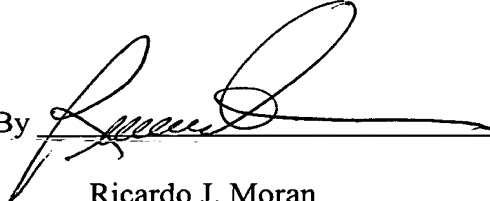
### III. CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date June 19, 2003

By 

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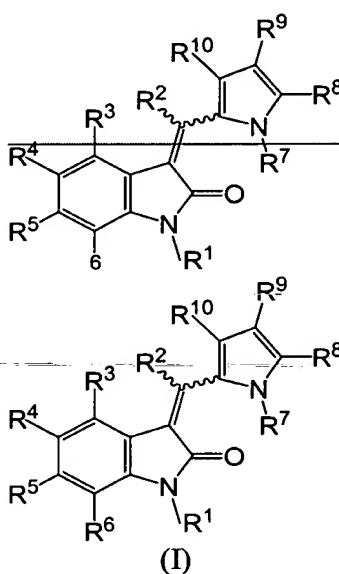
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**MARKED UP VERSION SHOWING CHANGES MADE**

1. (Twice amended) A formulation suitable for parenteral or oral administration, said formulation comprising an ionizable substituted indolinone of Formula (I):



wherein

$R^1$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

$R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and  $-NR^{11}R^{12}$ ;

$R^{11}$  and  $R^{12}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

$R^3$  and  $R^4$ ,  $R^4$  and  $R^5$ , or  $R^5$  and  $R^6$  may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

$R^7$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

$R^9$  is  $-(alk)_1Z$ , wherein  $Alk_1$  is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

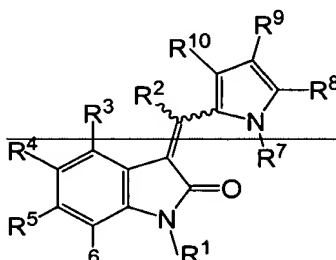
$R^8$  and  $R^9$ - $R^{10}$  are independently selected from hydrogen and unsubstituted lower alkyl;

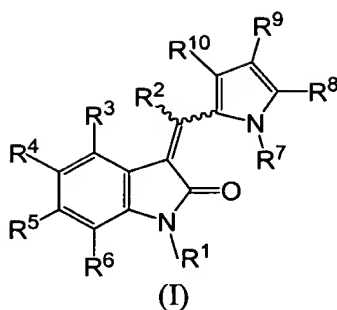
one or more polyoxyhydrocarbyl compounds; and

-a pharmaceutically acceptable carrier therefor;

wherein said ionizable substituted indolinone is solubilized by combining said indolinone with a molar equivalent of a base solution or an acid solution.

76. (Twice amended) A method of making a formulation suitable for oral administration comprising admixing an ionizable substituted indolinone of Formula (I):





wherein

$R^1$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

$R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and  $-NR^{11}R^{12}$ ;

$R^{11}$  and  $R^{12}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

$R^3$  and  $R^4$ ,  $R^4$  and  $R^5$ , or  $R^5$  and  $R^6$  may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

$R^7$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

$R^9$  is  $-(alk_1)Z$ , wherein  $Alk_1$  is selected from the group consisting of alkyl, alkenyl or alkynyl, and  $Z$  is a polar group;

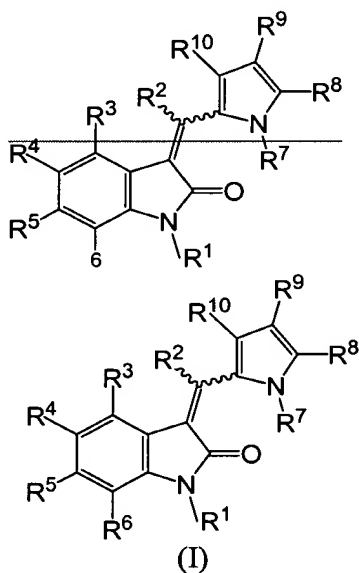
$R^8$  and  $R^{10}$  are independently selected from hydrogen and unsubstituted lower alkyl;

one or more pharmaceutically acceptable surfactants; and

one or more pharmaceutically acceptable oils.

78. (Twice amended) A method of treating a protein kinase related disorder in a patient in need of treatment comprising:

a.) diluting a parenteral formulation into a pharmaceutically acceptable solution, said parenteral formulation comprising an ionizable substituted indolinone of Formula (I);



wherein

$R^1$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;



$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

$R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and  $-NR^{11}R^{12}$ ;

$R^{11}$  and  $R^{12}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

$R^3$  and  $R^4$ ,  $R^4$  and  $R^5$ , or  $R^5$  and  $R^6$  may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

$R^7$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

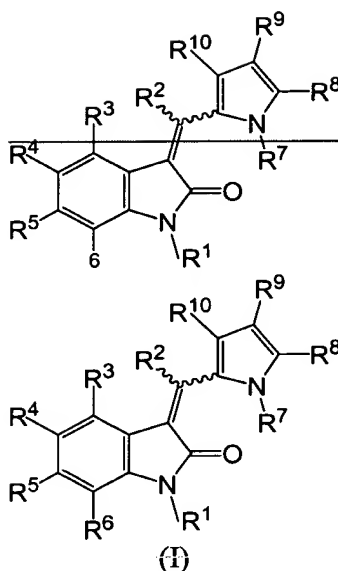
$R^9$  is  $-(alk_1)Z$ , wherein  $Alk_1$  is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

$R^8$  and  $R^9$ - $R^{10}$  are independently selected from hydrogen and unsubstituted lower alkyl, one or more polyoxyhydrocarbyl compounds, and

-a buffer; and

b.) parenterally administering said diluted formulation to said patient.

80. (Twice amended) A method of treating a protein kinase related disorder in a patient in need of treatment comprising orally administering to said patient a formulation comprising an ionizable substituted indolinone of Formula (I);



wherein

$R^1$  is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, hydroxy, alkoxy, C-carboxy, O-carboxy, acetyl, C-amido, C-thioamido, sulfonyl and trihalomethanesulfonyl;

$R^2$  is selected from the group consisting of hydrogen, halo, alkyl, cycloalkyl, aryl, heteroaryl and heteroalicyclic;

$R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are independently selected from the group consisting of hydrogen, alkyl, trihaloalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, arylthio, sulfinyl, sulfonyl, S-sulfonamido, N-sulfonamido, trihalomethane-sulfonamido, carbonyl, C-carboxy, O-carboxy, C-amido, N-amido, cyano, nitro, halo, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, amino and  $-NR^{11}R^{12}$ ;

$R^{11}$  and  $R^{12}$  are independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heteroaryl, carbonyl, acetyl, sulfonyl, trifluoromethanesulfonyl and, combined, a five- or six-member heteroalicyclic ring;

$R^3$  and  $R^4$ ,  $R^4$  and  $R^5$ , or  $R^5$  and  $R^6$  may combine to form a six-member aryl ring, a methylenedioxy group or an ethylenedioxy group;

$R^7$  is selected from the group consisting of hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, aryl, heteroaryl, heteroalicyclic, hydroxy, alkoxy, aryloxy, carbonyl, acetyl, C-amido, C-thioamido, amidino, C-carboxy, O-carboxy, sulfonyl and trihalomethane-sulfonyl;

$R^9$  is  $-(alk_1)Z$ , wherein  $Alk_1$  is selected from the group consisting of alkyl, alkenyl or alkynyl, and Z is a polar group;

$R^8$  and  $R^9$ - $R^{10}$  are independently selected from hydrogen and unsubstituted lower alkyl;

one or more pharmaceutically acceptable surfactants; and

-one or more pharmaceutically acceptable oils.